

## REMARKS

By this amendment, claim 12 is amended. Support for the amendment can be found in the specification, for example, at page 8, penultimate paragraph and in the original claims. No issue of new matter arises.

### *Claim Objection*

Claim 12 is amended to spell out the intended meaning of iRNA based on specification support at page 8, lines 26 and 27. No issue of new matter arises. Reconsideration and withdrawal of this objection are respectfully requested.

### *Rejections under 35 U.S.C. §112, second paragraph*

Claims 16, 17 and 45-48 were rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Applicants respectfully traverse this rejection.

The Office Action has cited post-filing art relating to antisense technology and to RNAi. Delivery and toxicity are cited as issue. Toxicity is an issue recited in the claims. Toxicological assessment is a complicated issue weighing risks and benefits that are properly weighed by the FDA. Thus toxicity is not a proper basis for rejection. With respect to delivery, Applicants wish to show that prior to the filing date, the state of the art showed delivery issues were addressable and could be obviated. Makimura et al., 2002 teaches that RNAi produced sequence specific reduction of gene expression in adult mice. Several additional articles showing success of the technology are cited in the article. Accordingly, in view of the state of the art as evidenced in Makimura and in Hanlon, discussed below, issues of delivery cannot properly be considered as raising the question of non-enablement.

The Office Action cites Hanlon: "The issue of delivery has restricted the antisense filed for almost two decades. It is possible to infuse backbone modified oligonucleotides *in vivo*, but achieving intracellular delivery at effective concentrations is a major challenge." This specifically speaks to past history relating to antisense as practiced in the previous decades. In the context of the article discussing RNAi, this observation of the long struggle can be read as showing promise for the new technology. Although delivery is recognized as a challenge and delivery might always be improved, the state of the art had produced methods for delivering the RNA molecules to the intended sites. Hanlon itself recognizes successful systemic delivery with liposomes (page 376, second column, first full paragraph); and using hydrodynamic protocols (page 376, first column, penultimate paragraph).

Another comment quoted in the Office Action relates to systemic delivery to T-lymphocytes. T-lymphocytes are not the target cell. The issue of numbers of T-cells is irrelevant. This issue of delivery to T-lymphocytes is not a properly raised issue. Thus the post filing art as cited by the Examiner may indicate that improvement is desirable. But a need for improvement is not a proper basis for rejection. The patent statutes do not set a standard of perfection as a requisite for patentability. In view of the above remarks reconsideration and withdrawal of this rejection are respectfully requested.

Claim 42 was rejected under 35 U.S.C. §112, first paragraph as allegedly lacking written description. Claim 42 is canceled. Reconsideration and withdrawal of this rejection are respectfully requested.

***Rejection under 35 U.S.C. §§102 and 103***

Claim 12 was rejected under 35 U.S.C. §102 and/or 35 U.S.C. §103 over Brown. Claim 12 is amended a) to recite complementarity rather than specifically hybridizes language thereby improving clarity of the broadest reasonable interpretation and b) to recite a minimum length of complementarity longer than 11. Reconsideration and withdrawal of this rejection are respectfully requested.

***Rejection under 35 U.S.C. §103***

Claims 12-17 and 45-48 were rejected under 35 U.S.C. §103 over Bailleul, Agrawal, Taylor, Bennet and Baracchini. Applicants respectfully traverse this rejection.

The Office Action states: "One cannot show non-obviousness by attacking references individually where rejections are based on combinations of references." Still the combination of references must contain references that teach or suggest all the claim limitations.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP §2143.

The references when combined fail to teach all the claimed limitations. Furthermore, the references when combined teach away from the instant invention on more than one occasion. To cherry pick specific teachings from the references to attempt to rebuild the invention at hand

clearly constitutes improper hindsight. The specification is not to be used as a template to craft a 35 U.S.C. §103(a) rejection. There must be some suggestion or motivation in the references themselves for the combination to create the invention at hand.

The *prima facie* case of obvious fails at least because the applied references fail to teach or suggest all the claim limitations. The references when combined cannot properly be alleged to teach more than the compilation of all the applied reference teachings. None of the references teach interfering RNA. Agrawal is alleged to suggest an oligonucleotide with hairpin structure resistant to nucleolytic degradation. Properties of the generic disclosure of Agrawal are considered latent characteristics, but as latent characteristics cannot be properly cited as a motivation to combine teachings.

Taylor, Bennett and Baracchini (with Bailleul) "are relied on as a whole for what they taught or suggested to one of skill in the art at the time the instant invention was made." Only Bailleul is discussed in further detail. Accordingly, Applicants provide no further comments with respect to these references. Baracchini and Bennett were previously applied for allegedly teaching motivation and expectation. Taylor was applied allegedly for general teachings relating to antisense oligonucleotides 7-30 nucleotides long.

Claim 12 as presently amended recites the SEQ ID No. 21 that is neither taught or suggested by the applied references either individually or in combination. Accordingly no *prima facie* case of obviousness is established. Reconsideration and withdrawal of this rejection are respectfully requested.


### ***Conclusion***

In view of the above amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance and request prompt issuance of a Notice of Allowance. If the Examiner wishes to suggest additional amendment that might put the application in even better condition for allowance he is invited to contact Applicants' representative at the telephone number listed below.

*Fees*

No fees are believed necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

Respectfully submitted,



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Aventis Docket No. FRAV2003/0005 US NP